The case under question reports spontaneous cerebellar hemorrhage in a 72-year-old man with a history of hypertension, lacunar stroke, and mild cognitive impairment. In the natural history of small vessel disease, the likely pathological situation causing this case, ischemic and hemorrhagic events, represents different expressions of the same underlying microangiopathy. These 2 phenotypes may require different therapeutic approaches. The concern in this patient, on statin therapy for ischemic stroke prevention, is that he now has an intracerebral hemorrhage (ICH). So, what should we do with statins when brain ischemia and hemorrhage are both on board?

Several years ago, neurologists feared this situation, and withdrawal was the main approach taken. At that time, we were probably influenced by the side effects observed in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels trial (high-dose statins increasing the risk of hemorrhagic stroke) and concerned about the association between low-density lipoprotein level and hemorrhagic stroke, claimed by many authors. However, changes are coming, and new evidence supports the notion that maintaining our patient on statin therapy may provide substantial benefits for several reasons.

First, the hypocholesterolemia–ICH association is not entirely convincing, particularly in the case of statin-induced hypocholesterolemia. A recent meta-analysis of 31 randomized controlled trials investigating statin therapy for primary and secondary prevention by McKinney et al (Stroke 2012) reported no significant difference in the incidence of ICH in the active treatment group versus controls (odds ratio [OR], 1.08; 95% confidence interval [CI], 0.88–1.32; P=0.47) or was ICH risk related to the degree of low-density lipoprotein reduction. In contrast, the total stroke risk (OR, 0.84; 95% CI, 0.78–0.91; P<0.0001) and all-cause mortality (OR, 0.92; 95% CI, 0.87–0.96; P=0.0007) were significantly reduced by statins. In another study by Lee et al (Korean J Intern Med, 2012), including 34,315 subjects with serum low-density lipoprotein determinations, statin use with low-density lipoprotein levels was not related to ICH, which mainly occurred in hypocholesterolemic subjects who were not taking statins.

Second, the neuroprotective role of statins, well established in experimental stroke models, could also argue against withdrawal. Simvastatin administered acutely after ICH protects blood–brain barrier integrity, as determined by MRI and correlative immunohistochemistry, better than other statins.

Finally, we should remember that we may want to protect our patient from a new ischemic stroke event, and statins do especially well in preventing progression of small vessel disease, as has been documented in the meta-analysis of Biffy et al (Stroke 2011).

Of course, numbers and theory are not the whole story. Certain diagnostic tests might refine our decision to keep our patient on statins, such as those that identify the causes of the hemorrhagic event. MRI study, including gradient echo T2*-weighted imaging, may be of interest to detect the presence and location of lacunae, white matter hyperintensities, and microbleeds. If deep lacunae point to hypertensive microangiopathy as the first pathogenic possibility, our prostatin decision would be reinforced, but cerebral amyloid angiopathy should be considered when a cortical microbleed pattern is seen. ApoE genotyping might also support our decision because the ApoE2 allele confers higher hemorrhagic risk. A Pittsburgh compound B positron emission tomography scan showing the amyloid load might also be informative. If these tests suggest that we face cerebral amyloid angiopathy–related ICH, we may want to take a more cautious approach because a relationship has been documented between statins and cortical microbleeds.
However, before deciding to stop statins, we would like to have a study showing that there is a relationship with progression of microbleeds, indicating some causality and not just an association. This is an especially critical point because statins remain a possible future choice in amyloid therapy, and simvastatin has proved to reduce inflammation associated with vaccination in aged Alzheimer mouse models.

In the case presented, we believe statin therapy should not be discontinued after ICH given its potential neuroprotective role, the evidence of good, long-term outcome when it is maintained, along with the deleterious effects of its suppression, and the lack of clear evidence proving an association with recurrent hemorrhagic events. If a particular statin should be chosen, simvastatin would probably be the right (or at least our) choice on the basis of its neuroprotective benefits. If you’re worried about amyloid, reduce the dose, but don’t renounce statins!

Disclosures

None.

References

Statin Therapy Should Not be Discontinued in Patients With Intracerebral Hemorrhage
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